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10/593,372	01/12/2007	Jean-Marie Ketelslegers	SONN129.001APC	8858

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EXAMINER	
GRUN, JAMES LESLIE	

ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/593,372	KETELSLEGERS ET AL.	
	Examiner	Art Unit	
	JAMES L. GRUN	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-98* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *19 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/26/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Claims 1-98 remain in the case.

The drawings are objected to for the following reasons: in Fig. 12, legend indicates a group B, yet figure is labeled with a curve C; in Fig. 15, curves are not labeled. Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.85(a). Submission of corrected drawings may no longer be held in abeyance pending the indication of allowable subject matter. Failure to take corrective action within the set period will result in **ABANDONMENT** of the application.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-98 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 and claims dependent thereupon, recitation of "the" survival, first marker, second marker, level, likelihood, or normal lack antecedent basis.

In claim 16 and claims dependent thereupon, "wherein said N-proANP is N-proANP (68-98)" does not properly further limit "N-proANP (1-98)"; it is believed "said N-proANP" --fragment-- was intended as that being further limited.

In claim 32, the subject matter of claim 24 having Big ET-1 or its fragments as the first marker is not being further limited by the subject matter of the instant claim wherein a different

marker is now claimed as the first marker; it is believed that N-proBNP or its fragments were intended as the --second-- marker.

In claim 54, "said" Big ET-1 (22-38) lacks antecedent support; it is believed the claim was intended to depend from claim --53-- rather than from "52".

In claim 67 and claims dependent thereupon, recitation of "the" survival, first marker, second marker, level, or likelihood lack antecedent basis.

In claim 91 and claims dependent thereupon, "wherein said first marker is N-proANP (1-98)" does not properly further limit the first marker being "proANP"; it is believed claim --89-- was intended as that being further limited.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 67, 68, 79-81, and 88 are rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Selvais et al. (Eur. J. Clin. Invest. 28: 636, 1998).

Selvais et al. (1998) analyzed the predictive value of plasma atrial natriuretic factor (ANF, i.e., ANP), N-proANP, and BNP for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure (see e.g. Table 1) and at least two of the peptides, N-proANP and BNP levels, were significantly associated with death in these patients (see e.g. page 638). Cut-offs were selected (see e.g. page 638) and used to determine, singly or in paired comparisons (see

Figs. 3 and 4), the risk of death in the patients grouped as NYHA class I-II and NYHA class III-IV.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
> (c) Subject matter developed by another person, which qualifies as prior art only under one or more subsections (e), (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1-98 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Selvais et al. (J. Cardiac Failure 6: 201, 2000), Selvais et al. (Eur. J. Clin. Invest. 28: 636, 1998), Rousseau et al. (Circulation 108 (17 Suppl.): IV-556, 2003), Berger et al. (J. Heart Lung Transplant. 22 : 1037, 2003), and Sabatine et al. (Circulation 105: 1760, 2002).

Selvais et al. (2000) analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANF, i.e., N-proANP), brain natriuretic peptide (BNP), and endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes II-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and all 3, especially ET-1 and N-proANP levels, were significantly associated with death in these patients (see e.g. Table 3). Cut-offs were selected and used to determine, singly or in paired comparisons (see

Table 3 and Figs. 1 and 2), the risk of death in the patients. The reference teaches that clinically useful prognostic information can be easily obtained by measuring ET-1 and cardiac natriuretic peptide concentrations in patients with congestive heart failure (¶ bridging pages 205-206). The reference also suggests big ET-1 as a more stable and easier molecule to measure than ET-1 (see e.g. page 205, col. 1).

Selvais et al. (1998) analyzed the predictive value of plasma atrial natriuretic factor (ANF, i.e., ANP), N-proANP, and BNP for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and at least two of the peptides, N-proANP and BNP levels, were significantly associated with death in these patients (see e.g. page 638). Cut-offs were selected and used to determine, singly or in paired comparisons (see Figs. 3 and 4), the risk of death in the patients.

Rousseau et al. analyzed the predictive value of plasma N-ANP (1-25), N-ANP (68-98), BNP, N-BNP, ET-1, and big ET-1 for survival in patients with severe congestive heart failure (NYHA classes III-IV). All the measured analytes except BNP were found to significantly predict survival, however both big ET-1 and ET-1 were strong independent predictors of survival in these patients. Cut-offs selected around the mean for big ET-1 ($\geq$ 12 pg/ml) and ET-1 (> 9 pg/ml) in the patients with severe congestive heart failure significantly predicted 5 year survival.

Berger et al. teach that endothelin and natriuretic peptides were known to have prognostic significance in chronic heart failure (CHF) and analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANP), N-terminal brain natriuretic peptide (N-proBNP), and big endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure

(NYHA classes I-IV). The reference teaches that the different markers have different significance depending upon the clinical stage and the time of the observation period, big endothelin being best for predicting 1 year prognosis in patients with severe CHF and the natriuretic peptides being better markers for 2-3 year prognosis in mild and moderate CHF.

Sabatine et al. teach that a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers enables clinicians to stratify risk for various prognoses, including death, in cardiac patients.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have determined various combinations of ET-1 and/or big ET-1 and/or cardiac natriuretic hormones and/or their fragments in the prediction of survival in patients with congestive heart failure because Selvais et al. (2000), Selvais et al. (1998), Rousseau et al., and/or Berger et al. teach the well-known significance of these determinations, singly or in different combinations, for the prediction of survival in cardiac patients, those with congestive heart failure in particular, and Berger et al. teaches that determinations of the different peptide hormones provide complementary or different clinical information depending upon the severity of heart failure in the patient and the length of the observation period. One of ordinary skill in the art would have been motivated to use the successful methods in combination in a method of prognosis prediction because determinations of these analytes had been taught individually or in the same combinations as instantly claimed or in different combinations by the prior art to be effective in the prediction of death in congestive heart failure patients and it would have been obvious to predict survival with multiple markers because the idea of doing so would have followed logically from their having been individually taught, as well as in the same or in other

combinations, in the prior art to be useful for the same purpose, and, in particular, it would have been obvious to combine the determinations and individual cut-offs for each analyte in view of the direct suggestions in Selvais et al. (2000) and Selvais et al. (1998) to do so. Moreover, one would have had further obvious motivation to use a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers as taught in Sabatine et al. for the benefits taught therein. It would have been further obvious to one of ordinary skill to have followed the guidance provided in the combined teachings of the references to determine an optimal cut-off value in each particular assay, since it has been held that: where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art (see *In re Aller*, 105 USPQ 233); and, discovering an optimum value of a result effective variable involves only routine skill in the art (see *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

Claims 67-98 are rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Tsutamoto et al. (Eur. Heart J. 20: 1799, 1999), Berger et al. (J. Heart Lung Transplant. 22 : 1037, 2003), Selvais et al. (Eur. J. Clin. Invest. 28: 636, 1998), Selvais et al. (J. Cardiac Failure 6: 201, 2000), Rousseau et al. (Circulation 108 (17 Suppl.): IV-556, 2003), and Sabatine et al. (Circulation 105: 1760, 2002).

Tsutamoto et al. measured plasma levels of atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) and endothelin-1 (ET-1) in patients with New York Heart Association functional class I-II mild heart failure. The levels were compared to those in normals and used to determine the significance of the analyte levels as predictors of mortality in these patients. A cut-off level of BNP approximately 3.7 fold above the normal level (see e.g. pages 1800 and 1801-2) indicated significantly elevated mortality risk.

Berger et al. teach that endothelin and natriuretic peptides were known to have prognostic significance in chronic heart failure (CHF) and analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANP), N-terminal brain natriuretic peptide (N-proBNP), and big endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). The reference teaches that the different markers have different significance depending upon the clinical stage and the time of the observation period, big endothelin being best for predicting 1 year prognosis in patients with severe CHF and the natriuretic peptides being better markers for 2-3 year prognosis in mild and moderate CHF.

Selvais et al. (1998) analyzed the predictive value of plasma atrial natriuretic factor (ANF, i.e., ANP), N-proANP, and BNP for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and at least two of the peptides, N-proANP and BNP levels, were significantly associated with death in these patients (see e.g. page 638). Cut-offs were selected and used to determine, singly or in paired comparisons (see Figs. 3 and 4), the risk of death in the patients.

Selvais et al. (2000) analyzed the predictive value of plasma N-terminal atrial natriuretic factor (N-proANF, i.e., N-proANP), brain natriuretic peptide (BNP), and endothelin-1 (ET-1) for survival in patients with mild to severe congestive heart failure (NYHA classes II-IV). Plasma concentrations of the 3 peptides increased with the severity of heart failure and all 3, especially ET-1 and N-proANP levels, were significantly associated with death in these patients (see e.g. Table 3). Cut-offs were selected and used to determine, singly or in paired comparisons (see Table 3 and Figs. 1 and 2), the risk of death in the patients. The reference teaches that clinically useful prognostic information can be easily obtained by measuring ET-1 and cardiac natriuretic peptide concentrations in patients with congestive heart failure (¶ bridging pages 205-206). The reference also suggests big ET-1 as a more stable and easier molecule to measure than ET-1 (see e.g. page 205, col. 1).

The teachings of Rousseau et al. are as set forth above in this Office action. The reference is cited as evidence that assays of N-terminal fragments (N-ANP (1-25), N-ANP (68-98)) of the N-terminal atrial natriuretic factor (N-proANP) provide predictive results similar to that provided by assays of the intact N-proANP known to the art such as those of Berger et al., Selvais et al. (1998), and/or Selvais et al. (2000).

Sabatine et al. teach that a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers enables clinicians to stratify risk for various prognoses, including death, in cardiac patients.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have determined various combinations of ET-1 and/or big ET-1 and/or cardiac natriuretic hormones and/or their fragments in the prediction of survival in patients with

mild congestive heart failure because Tsutamoto et al., Berger et al., Selvais et al. (1998), and/or Selvais et al. (2000), combined with the teachings of Rousseau et al., teach the well-known significance of these determinations, singly or in different combinations, for the prediction of survival in cardiac patients, those with congestive heart failure in particular, and Berger et al. teaches that determinations of the different peptide hormones provide complementary or different clinical information depending upon the severity of heart failure in the patient and the length of the observation period. One of ordinary skill in the art would have been motivated to use the successful methods in combination in a method of prognosis prediction because determinations of these analytes had been taught individually or in the same combinations as instantly claimed or in different combinations by the prior art to be effective in the prediction of death in mild congestive heart failure patients and it would have been obvious to predict survival with multiple markers because the idea of doing so would have followed logically from their having been individually taught, as well as in the same or in other combinations, in the prior art to be useful for the same purpose, and, in particular, it would have been obvious to combine the determinations and individual cut-offs for each analyte in view of the direct suggestions in Selvais et al. (2000) and Selvais et al. (1998) to do so. Moreover, one would have had further obvious motivation to use a simple multimarker approach using positive/negative cut-offs and the number of positive complementary markers as taught in Sabatine et al. for the benefits taught therein. It would have been further obvious to one of ordinary skill to have followed the guidance provided in the combined teachings of the references to determine an optimal cut-off value in each particular assay, since it has been held that: where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only

routine skill in the art (see *In re Aller*, 105 USPQ 233); and, discovering an optimum value of a result effective variable involves only routine skill in the art (see *In re Boesch*, 617 F.2d 272, 205 USPQ 215 (CCPA 1980)).

Thus, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Ruskoaho (Endo. Rev. 24: 341, 2003) teaches that "because plasma ANP, N-ANP, BNP, and N-BNP levels are increased in proportion to the severity of left ventricular dysfunction and in parallel with the activation of other neurohormonal systems, the association of cardiac hormones with prognosis in patients with chronic heart failure is an expected finding" (see page 347, col. 2).

Valdemarsson et al. (J. Int. Med. 235: 595, 1994) analyzed the predictive value of plasma atrial natriuretic factor (ANP) for survival in patients with mild to severe congestive heart failure (NYHA classes I-IV).

Clerico et al. (Horm. Metab. Res. 31: 487, 1999) teach that determining the plasma levels of ANP, BNP, and/or N-terminal-derived fragments of the prohormones provide complementary or different clinical information (see e.g. page 491, col. 1, last ¶). The reference teaches that in 1999 "the importance of measuring the circulating levels of cardiac natriuretic hormones in . . . predicting mortality/survival rates is now well known" (see page 493, col. 2).

Asada et al. (US 6,828,107) teaches that levels of BNP in heart failure patients can be detected as increased several tens to several hundreds times that of healthy normal subjects (see e.g. col. 1).

Tsutamoto et al. (American J. Cardiol. 76: 803, 1995) teach that plasma endothelin-1 (ET-1) levels increased with the severity from mild to severe congestive heart failure (NYHA classes II-IV) (see e.g. page 805 and Fig. 2) and analyzed the predictive value of a plasma ET-1 cut-off level for survival in these patients (see e.g. page 806 and Fig. 6).

Stanek et al. (Trans. Proc. 29: 595, 1997) teach big ET-1 levels as a predictor of survival in NYHA class II-IV heart failure patients.

Hülsmann et al. (J. Am. Coll. Cardiol. 32: 1695, 1998) analyzed the predictive value of plasma atrial natriuretic peptide (ANP) and big endothelin-1 (ET-1) levels for survival in patients with congestive heart failure.

Buechler et al. (US 2004/0121343) teach multimarker panels for differential diagnosis.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to James L. Grun, Ph.D., whose telephone number is (571) 272-0821. The examiner can normally be reached on weekdays from 9 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya, SPE, can be contacted at (571) 272-0806.

The phone number for official facsimile transmitted communications to TC 1600, Group 1640, is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application, or requests to supply missing elements from Office communications, should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/J. L. G./
James L. Grun, Ph.D.
Examiner, Art Unit 1641
September 26, 2009

/Ann Y. Lam/
Primary Examiner, Art Unit 1641
September 24, 2009